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Family history and risk of stomach cancer in Warsaw, Poland

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In a population-based case–control study of stomach cancer conducted in Warsaw, Poland, 464 cases and 480 controls were interviewed to evaluate the role of family history and other risk factors. A greater than threefold increase in risk was associated with a history of stomach cancer in a first degree relative (OR = 3.5; 95% CI = 2.0–6.2), but no excess risk was seen with other forms of cancer. The risk associated with familial occurrence was not significantly modified by gender, age or ABO blood type, and did not vary with Laurén histologic classification. Our findings add to evidence for a familial predisposition to both diffuse and intestinal types of gastric cancer. Further studies are needed to identify the susceptibility genes and environmental exposures that may account for the familial tendency to stomach cancer.

Key words: Case–control study, family history, Poland, stomach cancer.

Introduction

While epidemiological evidence has suggested a major role for environmental factors in gastric carcinogenesis, genetic factors also appear to influence risk. As early as 1953, Aird *et al.* (1953) noted that blood group A was more common among stomach cancer patients than the general population. More recently, both cohort and case–control studies have documented an excess risk of stomach cancer associated with a positive family history among siblings and parents, with risk increasing with the number of relatives affected (Ihamaki *et al.* 1991; Ogawa *et al.*, 1985; Mecklin *et al.*, 1988; La Vecchia *et al.*, 1992; Palli *et al.*, 1994; Nagase *et al.*, 1996). Familial clustering of premalignant gastric lesions has also been shown in studies based on endoscopy screening (Bonney *et al.*, 1986; Zhao *et al.*, 1994). When gastric tumors are analyzed by the Laurén histologic classification (Laurén, 1965), genetic factors appear largely responsible for the diffuse type, which has been associated with blood group A and with a familial tendency recently linked to germline mutations of *E-cadherin* gene (Guilford *et al.*, 1998; Gayther *et al.*, 1998). In contrast, environmental determinants such as *Helicobacter pylori* infection appear to account for the intestinal type, which predominates in high-risk areas (Parsonnet *et al.*, 1991; Laurén and Nevalainen, 1993).

To further clarify risk factors for stomach cancer, we conducted a population-based case–control study in Warsaw, Poland, where incidence and mortality

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rates of this tumor are among the highest in Europe (Zatonski and Tyczynski, 1996; Parkin *et al.*, 1997). In 1996, the incidence rates in Poland were 18.2 per 100,000 men and 7.1 per 100,000 women, whereas the mortality rates were 17.9 and 6.7 per 100,000 men and women, respectively (Zatonski and Tyczynski, 1996). Here we examine the relationships between family history of cancer, ABO blood group and risk of gastric cancer according to the Laurén classification.

Material and methods

The data were derived from a population-based case–control study of stomach cancer carried out in Warsaw, Poland, during 1994 to 1996. The design of this study has been described in detail elsewhere (Chow *et al.*, 1999). Briefly, 464 patients newly diagnosed with stomach cancer between 1 March 1994 and 30 April 1996 and 480 randomly-selected population controls were recruited, representing 90.1% and 87.4% of eligible patients and controls, respectively. The controls were frequency-matched to cases by gender and age. All cases were diagnosed by endoscopy or surgery, and 90.2% were confirmed by histology.

In-person interviews with controls and cases (or next of kin for 140 cases (27.2%) who were deceased or too ill to be interviewed in person) were conducted by trained interviewers, whenever possible in the subject's home. A structured questionnaire sought information on demographic characteristics, living conditions during early adolescence, food frequency history and preparation methods, cigarette smoking, alcohol drinking, medical history, occupational history, and history of cancer in first degree family members (parents, full siblings, and children). Information was collected on the anatomic site of cancer, date of diagnosis, and age at diagnosis for each affected first-degree relative. The total number of siblings and children were also obtained.

To the extent possible, information on ABO blood group was extracted from medical records for cases and from government-issued personal identification cards for all participants. For those with missing information, an ABO assay was performed. Cases were classified according to the Laurén classification by two study pathologists, one in Poland (A Nasierowska-Guttmejer) and the other in the USA (FD Groves), with discrepancies decided by a senior pathologist at the US Armed Forces Institute of Pathology (LH Sobin). Any case that could not be clearly identified as intestinal or diffuse type was designated as 'indeterminate'.

The risks associated with family history of cancer were estimated by odds ratios (ORs) and corresponding 95% confidence intervals (CIs) using logistic regression methods (Breslow and Day, 1980). All ORs were adjusted for age (<50, 50–59, 60–69, 70 +), gender, educational level (≤primary school graduate, high school–some college, ≥college graduate), cigarette smoking pack-years (continuous), and intake of fresh fruits/vegetables (quartile categories) as well as the number of first degree relatives. Further adjustment for caloric intake, body mass index, alcohol drinking, *Helicobacter pylori* infection, and number of years lived on a farm did not materially alter the risk estimates, and thus were not included in the final models. Effect modification by gender, age, and ABO blood group was examined by adding an interaction term in the model.

Results

The cases and controls were similar in distribution by age (72.4% of cases and 71.2% of controls were aged 60 or older) and gender (65.1% of cases and 65.4% of controls were male). The controls, however, were slightly better educated than cases (27.5% vs 19.2% were college graduates). Information on family history of cancer was unavailable for 27 (5.8%) cases and 8 (1.7%) controls. Cases with information on family history had similar distributions by gender, age, education, ABO blood group, anatomic subsite, and histologic type according to the Laurén classification, but had fewer proxy respondents than cases without such information.

Among 437 cases and 472 controls with known family history, the average numbers of first degree relatives reported by cases and controls were identical (mean = 6.6, median = 6.0). Overall, 176 cases (37.9%) and 154 controls (32.1%) reported a history of cancer in a first degree relative. Of these, 59 cases (33.5%) and 19 controls (12.3%) reported a family history of stomach cancer, yielding a greater than threefold excess risk (OR = 3.5; CI: 2.0–6.2) (Table 1). Four cases and no controls reported more than one close relative with stomach cancer. Excluding stomach cancer, no association was seen for a family history of other gastrointestinal cancer (OR = 0.8) or all other cancers combined (OR = 1.0). Risk was unrelated also to the number of relatives diagnosed with non-gastric cancer (data not shown).

Table 1. Odds ratios (ORs) and 95% confidence intervals (CIs) of stomach cancer in relation to family history of cancer, Warsaw, Poland, 1994–96

Family history	No. of cases	No. of controls	OR*	(95% CI)
Any cancer				
No	261	318	1.0	
Yes	176	154	1.4	(1.0–1.9)
Stomach cancer				
No	378	453		1.0
Yes	59	19	3.5	(2.0–6.2)
Any gastrointestinal cancer excluding stomach				
No	393	410	1.0	
Yes	44	62	0.8	(0.5–1.2)
Any other than stomach cancer				
No	309	333	1.0	
Yes	128	139	1.0	(0.7–1.3)

*Adjusted for: age, sex, education, cigarettes (pack-years), fresh fruits/vegetables(quartiles).

For subjects with a family history of stomach cancer, the risk was more than twofold (OR = 2.4; CI: 1.1–4.5) when a parent was affected, the risks being higher with an affected mother (OR = 3.0; CI: 1.0–8.6) than father (OR = 1.8; CI: 0.7–4.5). However, the risk was highest when a sibling was affected (OR = 6.7; CI: 2.5–18.0) (Table 2).

Effect modification of family history of stomach cancer was examined in Table 3. The ORs associated with positive family history were higher among men than women, and among those aged 60 years or older than those under 60 years of age, although the interaction with gender or age was not statistically significant. In addition, when stratified by blood type, the ORs associated with positive family history were slightly but not significantly higher among those with blood group O than those with blood group A or other types (B and AB). However, in the overall study, blood type A was associated with a slightly elevated risk (OR = 1.2; 95% CI: 0.6–1.8) relative to other types. When stratified by Laurén histology, elevated risks were observed for both the intestinal type (OR = 4.0; 95% CI: 2.2–7.2) and the diffuse type (OR = 2.1; 95% CI: 0.7–6.9), although the latter association did not reach statistical significance. Similar risks were observed for tumors arising from different subsites of the stomach (i.e. cardia vs other).

The results were essentially unchanged after excluding cases diagnosed by surgery/endoscopy without microscopic confirmation or cases with proxy interviews from the analyses (data not shown). From calculations of attributable risk (Hennekens and Buring, 1987), we estimate that the proportion of stomach cancer in Warsaw due to familial predisposition is 10%, while the proportion related to blood type A is 7%.

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) of stomach cancer in relation to family history of stomach cancer by type of relatives, Warsaw, Poland, 1994–96

Family history of stomach cancer	No. of cases	No. of controls	OR*	95% CI
Parental history				
No	406	458	1.0	
Yes	31	14	2.4	(1.1–4.5)
Sex of parent affected				
None	406	458	1.0	
Father	15	9	1.8	(0.7–4.5)‡
Mother	16	5	3.0	(1.0–8.6)
Siblings history				
No	408	467	1.0	
Yes	29	5	6.7	(2.5–18.0)†
Sex of siblings affected				
None	408	467	1.0	
Male	15	3	5.4	(1.5–19.5)
Female	13	2	8.2	(1.8–37.8)
Both	1	0	–	

*Adjusted for: age, sex, education, cigarettes (pack-years), fresh fruits/vegetables (quartiles).
‡Additional adjustment for siblings history and number of siblings.
†Additional adjustment for parental history and number of siblings.

Table 3. Odds ratios (ORs) and 95% confidence limits (CIs) of stomach cancer in relation to family history of stomach cancer, stratified by gender, age, blood group and Laurén histologic type, Warsaw, Poland, 1994–96

	Family history	Cases	Controls	OR*	95% CI
Male	No	240	296	1.0	
Female	Yes	42	11	4.6	(2.2–9.5)
	No	138	157	1.0	
	Yes	17	8	2.2	(0.8–5.7)
Age					
<60	No	120	133	1.0	
	Yes	8	5	1.8	(0.6–5.5)
60 +	No	285	328	1.0	
	Yes	51	14	4.2	(2.3–7.9)
Blood group					
A	No	154	158	1.0	
	Yes	25	8	3.2	(1.3–8.1)
O	No	111	157	1.0	
	Yes	15	6	4.5	(1.6–12.8)
B/AB	No	99	121	1.0	
	Yes	13	4	3.4	(1.0–11.5)
Laurén histology					
Intestinal	No	286	453	1.0	
	Yes	24	19	4.0	(2.2–7.2)
Diffuse	No	38	453	1.0	
Indeterminate	Yes	28	19	2.1	(0.7–6.9)
	No	44	453	1.0	
	Yes	7	19	6.0	(2.0–18.1)

*Adjusted for age, sex, education, cigarettes (pack-years), fresh fruits/vegetables.

Discussion

Our population-based case–control study of stomach cancer in Warsaw, Poland revealed a 3.5-fold increased risk among individuals whose first degree relative was similarly affected. The findings are consistent with previous studies of stomach cancer showing twofold or greater excess risks associated with a family history of stomach cancer, but not of other cancers (Zanghieri *et al.*, 1990; La Vecchia *et al.*, 1992; Palli *et al.*, 1994; Nagase *et al.*, 1996; Inoue *et al.*, 1998).

It has been suggested that the diffuse type of stomach cancer is influenced by genetic factors, while the intestinal type is mainly environmental in origin (Lethola, 1978; Mecklin *et al.*, 1988; Parsonnet *et al.*, 1991; Laurén and Nevalainen, 1993). In our study, risk of both diffuse and intestinal types of tumors were elevated with a family history of stomach cancer. A familial tendency to both types of stomach cancer has been reported in some previous studies (Zanghieri *et al.*, 1990; Palli *et al.*, 1994), but not in all (Kato *et al.*, 1990; Kikuchi *et al.*, 1996). In a recent Japanese study, the risk associated with family history of stomach cancer appeared to vary by subsite, with an excess risk of cardia cancer associated with a maternal history of stomach cancer (Inoue *et al.*, 1998). While we observed a slightly higher risk associated with maternal than paternal history of stomach cancer, there was no appreciable difference by subsite. The higher risk associated with gastric cancer in siblings than in parents suggests that a recessive mode of inheritance may contribute to some cases, or that shared childhood environmental exposures such as poor living conditions and *Helicobacter pylori* infection at early age may be involved (Webb *et al.*, 1994; Blaser *et al.*, 1995).

In our study, family history of stomach cancer was a stronger risk factor than having blood type A, which was associated with a non-significant 20% increased risk. Assuming a causal relation, based on the repeated findings of higher risk of stomach cancer among individuals with blood type A (Nomura, 1996), we estimate that the fraction of cases linked to blood type A is small (7%) but only slightly less than the fraction attributable to familial predisposition (10%).

A few limitations of our study should be considered in interpreting the findings. Given the disease status of the cases, recall or reporting bias is a concern in our interview-based data. However, a methodological study by Love *et al.* (1985) revealed that the primary cancer site among first degree relatives was correctly identified by 83% of cancer patients, suggesting that information on family history is generally reported accurately by patients. Nevertheless, cases may be more likely to report that a relative has 'stomach cancer' when the true site of origin is elsewhere in the abdomen (Airewele *et al.*, 1998). The slightly inverse association with a family history of other gastrointestinal cancers in our study suggests that reporting bias may have contributed to the familial risk of stomach cancer, but only to a limited extent. Further, the proportion reporting a family cancer history in our study was similar for cases interviewed in person vs those by proxy. In a separate reliability study among a subset (112 of 324 directly interviewed) of our cases, we found good overall agreement ranging from 79.6% to 92.9% in reported family history of various cancers between cases and their next of kin. The similarity between self-reported and proxy-reported family histories suggests that recall of such information by cases is not affected by the illness.

Risks associated with a family history of cancer may be influenced by case–control differences in family size and the age distribution of relatives. In our study, the mean and median number of first degree relatives were identical for cases and controls. While we did not collect information on age of relatives, the relatively advanced ages among study subjects (mean age of 63.8 years for cases and 63.7 years for controls, and median age of 66 years for both cases and controls) suggest that most first degree relatives would have reached the age groups with high cancer incidence. Furthermore, the mean age of relatives diagnosed with cancer was similar between cases and controls.

Strong support for familial predisposition to gastric cancer is provided by studies in high-risk areas such as Colombia, South America (Bonney *et al.*, 1986) and Shandong, China (Zhao *et al.*, 1994). In these studies, familial clustering of precancerous lesions was determined by gastroscopy, rather than interviews. In addition, first degree relatives of gastric cancer patients are reported to have increased cell proliferation in gastric mucosa relative to dyspeptic controls (Meining *et al.*, 1998), while microsatellite instability in gastric cancer has been associated with familial susceptibility and blood type A (Ottini *et al.*, 1997). Of special importance is the recent discovery of germline mutations of the *E-cadherin* gene in some families prone to the diffuse type of stomach cancer (Guilford *et al.*, 1998; Gayther *et al.*, 1998). However, the familial tendency in our study extended to the

intestinal as well as the diffuse types, indicating the need to search for other susceptibility genes and environmental exposures that may account for the familial tendency to gastric cancer.

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References

Aird I, Bentall HH, Roberts JAF (1953). A relationship between cancer of stomach and the ABO blood groups. *BMJ* **1**: 799–801.

Airewele G, Adatto P, Cunningham J *et al.* (1998). Family history of cancer in patients with glioma: a validation study of accuracy. *J Natl Cancer Inst* **90**: 543–4.

Blaser MJ, Chyou PH, Nomura A (1995). Age at establishment of *Helicobacter pylori* infection and gastric carcinoma, gastric ulcer, and duodenal ulcer risk. *Cancer Res* **55**: 562–5.

Bonney GE, Elston RC, Correa P *et al.* (1986). Genetic etiology of gastric carcinoma. I. Chronic atrophic gastritis. *Genetic Epidemiol* **3**: 213–24.

Breslow NE, Day NE (1980). *Statistical methods in cancer research. Vol.1 The analysis of case–control studies*. IARC Scientific Publications No 32, Lyon.

Chow WH, Swanson C, Lissowska J *et al.* (1999). Risk of stomach cancer in relation to consumption of cigarette, alcohol and beverage in Warsaw, Poland. *Int J Cancer* (in press).

Gayther SA, Gorringe KL, Ramus SJ *et al.* (1998). Identification of germ-line *E-cadherin* mutations in gastric cancer families of European origin. *Cancer Res* **58**: 4086–9.

Guilford P, Hopkins J, Harraway J *et al.* (1998). E-cadherin germline mutations in familial gastric cancer. *Nature* **392**: 402–5.

Hennekens CH, Buring JE (1987). *Epidemiology in medicine*. Little Brown and Company, Boston, pp. 90–3.

Ihamaki T, Varis K, Kekki M, Siurala M. (1991). Characteristics of gastric mucosa which precede occurrence of gastric malignancy: results of long-term follow-up of three family samples. *Scand J Gastroenterol* **26(Suppl 186)**: 16–23.

Inoue M, Tajima K, Yamamura Y *et al.* (1998). Family history and subsite of gastric cancer: data from a case-referent study in Japan. *Int J Cancer* **76**: 801–5.

Kato I, Tominaga S, Ito Y *et al.* (1990). A comparative case–control analysis of stomach cancer and atrophic gastritis. *Cancer Res* **50**: 6559–64.

Kikuchi S, Nakajima T, Nishi T *et al.* (1996). Association between family history and gastric carcinoma among young adults. *Jpn J Cancer Res* **87**: 332–6.

La Vecchia C, Negri E, Franceschi S, Gentile A (1992). Family history and risk of stomach cancer and colorectal cancer. *Cancer* **70**: 50–55.

Laurén P (1965). The two histological main types of gastric cancer: diffuse and so-called intestinal type carcinoma. *Acta Pathol Microbiol Scand* **64**: 31–49.

Laurén PA, Nevalainen TJ (1993). Epidemiology of intestinal and diffuse types of gastric carcinoma. *Cancer* **71**: 2926–33.

Lethola J (1978). Family study of gastric carcinoma; with special reference to histological types. *Scand J Gastroenterol* **13(Suppl 50)**: 1–54.

Love RR, Evans AM, Josten DM (1985). The accuracy of patient reports of family history of cancer. *J Chron Dis* **38**: 289–93.

Mecklin JP, Nordling S, Saario I (1988). Carcinoma of stomach and its heredity in young patients. *Scand J Gastroenterol* **23**: 307–11.

Meining A, Hackelsberger A, Daenecke C *et al.* (1998). Increased cell proliferation of the gastric mucosa in first-degree relatives of gastric carcinoma patients. *Cancer* **83**: 876–81.

Nagase H, Ogino K, Yoshida I *et al.* (1996). Family history-related risk of gastric cancer in Japan: a hospital-based case–control study. *Jpn J Cancer Res* **87**: 1025–9.

Nomura A (1996). Stomach cancer. In *Cancer epidemiology and prevention* (2nd edn) (eds Schottenfeld D, Fraumeni JF Jr); Oxford University Press, New York, pp. 707–24.

Ogawa H, Kato I, Tominaga S (1985). Family history of cancer among cancer patients. *Jpn J Cancer Res* **76**: 113–18.

Ottini L, Palli D, Falchetti M *et al.* (1997). Microsatellite instability in gastric cancer is associated with tumor location and family history in a high-risk population from Tuscany. *Cancer Res* **57**: 4523–9.

Palli D, Galli M, Caporaso NE *et al.* (1994). Family history and risk of stomach cancer in Italy. *Cancer Epidemiol Biomarkers Prev* **3**: 15–18.

Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J (1997). *Cancer incidence in five continents*, Vol VII. IARC Scientific Publications No. 143. International Agency for Research on Cancer, Lyon.

Parsonnet J, Vandersteen D, Goates J *et al.* (1991). *Helicobacter pylori* infection in intestinal- and diffuse type gastric adenocarcinomas. *J Natl Cancer Inst* **83**: 640–3.

Webb PM, Knight T, Greaves S *et al.* (1994). Relation between infection with *Helicobacter pylori* and living conditions in childhood: evidence for person-to-person transmission in early life. *Br Med J* **308**: 750–3.

Zanghieri G, Di Gregorio C, Sacchetti C *et al.* (1990). Familial occurrence of gastric cancer in the 2-year experience of a population-based registry. *Cancer* **66**: 2047–51.

Zatonski W, Smans M, Tyczynski J, Boyle P (1996). *Atlas of cancer mortality in central Europe*. IARC Scientific Publication No 134, IARC, Lyon.

Zatonski W, Tyczynski J (1999). *Cancer in Poland in 1996*. The Maria Sklodowska-Curie Memorial Cancer Center, Department of Epidemiology and Cancer Prevention, National Cancer Registry, Warsaw, Poland.

Zhao L, Blot WJ, Liu WD *et al.* (1994). Familial predisposition to precancerous gastric lesions in a high-risk area of China. *Cancer Epidemiol Biomarkers Prev* **3**: 461–4.